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(54) Title: TREATMENT OF DIABETES

(57) Abstract

A method is provided for treating insulin-requiring diabetes by a regimen including administration of insulin and glucagon-like insulinotropic peptide or a related peptide.

TREATMENT OF DIABETES

Field of the Invention

The present invention relates to methods and compositions for treatment of diabetes.

Background of the Invention

The recent findings of the Diabetes Control and Complications Trial (DCCT) carried out by the U.S. National Institute of Health have emphasised the importance of doing everything possible to normalise blood glucose levels in diabetics to avoid or delay micro-vascular damage. Intensified insulin therapy has been shown by the trial to improve glycaemic control but is accompanied by the risk of hypoglycaemia. This limits the degree of glycaemic control which can be safely attempted, so that true normalisation of blood glucose levels cannot be achieved with insulin therapy alone.

Glucagon-like peptide 1(7-36)amide or glucagon-like insulinotropic peptide (GLIP) is a gastrointestinal peptide which potentiates insulin release in response to glycaemia in normal humans.

Glucagon-like insulinotropic peptide has been suggested for use either alone or in conjunction with oral hypoglycaemic agents in Type II or non-insulin dependent diabetes (Gutniak et al., (1992), N.E.J.M. vol. 326, p. 1316; International Patent Application No. WO93/18786). These authors have noted a synergistic effect between the peptide and oral hypoglycaemic agents in Type II diabetics.

The present inventor has found, unexpectedly, that administration of glucagon-like insulinotropic peptide permits improved glycaemic control in subjects with insulin-requiring diabetes.

Summary of Invention

In accordance with one embodiment of the present invention, a method is provided for treating insulin-requiring diabetes in a mammal comprising administering to the mammal in a suitable regimen an effective amount of insulin and an effective amount of a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b).

In accordance with a further embodiment of the invention, a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b) is used for the preparation of a medicament for use in the treatment of insulin-requiring diabetes in a suitable regimen which additionally comprises treatment with insulin.

In accordance with a further embodiment of the invention, a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b) is used for the preparation of a medicament which also includes insulin for treatment of insulin-requiring diabetes.

In accordance with a further embodiment of the invention, a pharmaceutical composition is provided for the treatment of insulin-requiring diabetes comprising an effective amount of a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b) and a pharmaceutically acceptable carrier.

In accordance with a further embodiment of the invention, a method is provided for treating Type I diabetes in a mammal comprising administering to the mammal an effective amount of a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b).

In accordance with a further embodiment of the invention, a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b) is used for the preparation of a medicament for use in the treatment of Type I diabetes.

Summary of Drawings

Figure 1A shows blood levels of glucose, Figure 1B shows C-peptide, Figure 1D shows human pancreatic polypeptide (HPP), Figure 1D shows glucagon and Figure 1E shows gastrin in Type I diabetic subjects after Sustacal meal alone (○) or Sustacal meal with GLIP infusion (●).

Figure 2A shows blood levels of glucose and Figure 2B C-peptide in Type I diabetic subjects during glucose infusion alone (○) or along with IV GLIP(●).

Figure 3A shows blood levels of glucose (expressed as the change (Δ) from baseline values at time zero) and Figure 3B shows C-peptide (expressed as the change (Δ) from baseline values at time zero) in Type I diabetic subjects after Sustacal meal and saline infusion (○) or Sustacal meal with infusion of 0.75 pm GLIP/kg/min (▲).

Figure 4A shows blood levels of glucose, Figure 4B shows C-peptide, Figure 4C shows insulin and Figure 4D shows human pancreatic polypeptide (HPP) in normal subjects after Sustacal meal alone (○) or Sustacal meal immediately preceded by a subcutaneous injection of 100 μg GLIP (●).

Figure 5A shows blood levels of glucose, Figure 5B shows C-peptide, Figure 5C shows insulin and Figure 5D shows human pancreatic polypeptide (HPP) in Type I diabetic subjects after Sustacal meal alone (○) or Sustacal meal immediately preceded by a subcutaneous injection of 100 μg GLIP (●).

Figure 6A shows blood levels of glucose, Figure 6B shows C-peptide, Figure 6C shows insulin, Figure 6D shows human pancreatic polypeptide (HPP), Figure 6E shows GLIP (GLIP-1) and Figure 6F gastrin in a Type I diabetic subject who received 5 Units regular human insulin and 50 μg GLIP subcutaneously prior to a Sustacal meal.

Detailed Description of the Invention

The glucagon-like peptide 1 fragments, glucagon-like peptide 1(7-36)amide and glucagon-like peptide 1(7-37), show essentially similar insulinotropic and other biochemical effects in humans and other mammals.

Glucagon-like peptide 1(7-36)amide is referred to herein as GLIP.

The present invention provides a method of treating Type I diabetes by administration of an effective amount of GLIP, or other glucagon-like peptide 1-related peptide, either alone or in conjunction with a regimen of insulin administration.

Although the discussion herein refers to use of "GLIP", it will be understood by those skilled in the art that the therapeutic methods of the invention may be practised by employing GLIP, glucagon-like peptide 1(7-37), an effective peptide including GLIP or glucagon-like peptide 1(7-37), or an effective fragment or analogue of GLIP or glucagon-like peptide 1(7-37).

As is seen in Figure 2, IV administration of GLIP along with intravenous glucose stimulated secretion of endogenous insulin in the subjects studied and gave improved control of blood glucose level. These subjects were in the remission phase, or so-called "honeymoon phase", of IDDM characterised by substantial remaining endogenous insulin secretion.

The same dose of GLIP (1.2 pm/kg/min) gave excellent control of blood glucose level in these subjects after a meal, as seen in Figure 1, Panel A. Under these conditions, GLIP infusion also prevented a significant increase in blood levels of C-peptide.

After the Sustacal meal, the test subjects showed normal secretion of pancreatic polypeptide (PP) but this response was absent during GLIP infusion (Figure 1, Panel C). It is believed that this abrogation of PP response was due to the delayed passage of the meal from the stomach to the small intestine as a result of GLIP administration. That it was not due to a general suppression of gastrointestinal peptide secretion is indicated by the normal gastrin response to the presence of food in the stomach in these subjects (Figure 1, Panel E).

Administration of GLIP prevented the mean rise in plasma glucagon levels stimulated by the meal in the absence of GLIP. Gastrin levels were not significantly affected.

Administration of a lower dose of GLIP (0.75 pmol/kg/min) along with a meal resulted in some increase in blood glucose and C-peptide, as seen in Figure 3. Although the increase in glucose was less than in the control experiment, the rise in C-peptide was similar to the control experiment.

GLIP is known to cause delay of gastric emptying in humans and other mammals (Wettergren et al., (1993), Digestive Diseases and Sciences, v. 38, p. 665). As seen in Figure 4, when GLIP is given subcutaneously to normal

subjects prior to ingestion of a meal, there is a delay of 30 to 60 minutes in the rise in blood glucose level. This delay is likely due to inhibition of gastric emptying.

When Type I diabetics were given GLIP subcutaneously prior to ingestion of a test meal, a lowering of blood glucose levels was seen compared to the control figures when no GLIP was administered (Figure 5, Panel A). The delayed rise in pancreatic polypeptide (HPP) levels (Panel D) indicate delayed gastric emptying. As seen from Panels B and C, there was no enhancement of insulin secretion over control levels to account for the lower glucose levels.

It may be that the improved glycaemic control seen with GLIP administration in Type I diabetics is due to delay of the post-meal rise in blood glucose through the interval required for the establishment of the effect of insulin.

The efficacy of GLIP administration along with insulin in restraining the expected rise in blood glucose after a standard meal in Type I diabetes is seen in Example 6 and Figure 6. 50 μg GLIP was administered along with half the insulin dose that would usually be required to deal with the test meal. As seen in Figure 6, Panel A, blood glucose did not rise above 8 mM. With this size of meal and half the usual insulin dose, considerably higher blood glucose levels would have been expected, in the absence of the effect of GLIP. For example, with this meal and no insulin, blood glucose levels reached 15 mM, as seen in Figure 5, Panel A.

As seen from Figure 6, Panel E, GLIP was cleared from the blood in about two hours so that pre-meal GLIP administration would not be expected to interfere with management of subsequent meals.

When GLIP is used to improve glycaemic control in Type I diabetics having residual endogenous insulin secretion capacity, both the insulinotropic effect of the

hormone and its effect to delay gastric emptying will contribute to its effect. Some remission phase Type I subjects may be sufficiently controlled by administration of GLIP alone, without exogenous insulin.

In the majority of patients with Type I diabetes, however, treatment with a regimen including both GLIP and insulin is likely to be required. These studies indicate that the observed effects of GLIP on glycaemia are not dependent on stimulation of insulin release and are therefore not limited to diabetics retaining residual insulin secreting capacity.

The use of GLIP in treating Type I diabetes, in accordance with the present invention, provides improved glycaemic control and reduces post-prandial excursions of blood glucose. This accords with the current emphasis on normalising blood glucose levels as much as possible, to reduce diabetic complications.

Furthermore, a regimen combining administration of insulin and administration of GLIP, in accordance with the present invention, is applicable to patients with insulin requiring diabetes which would not strictly be classified as Type I.

An insulin-requiring diabetic is a diabetic who is unable to avoid hyperglycaemia without the use of insulin. The invention further provides a method for treating patients with diabetes which is etiologically Type II but requires insulin treatment.

Diabetics frequently find the requirements for food intake and insulin administration at midday particularly irksome and an interference with work and other activities. By administering GLIP to diabetic subjects at breakfast time, along with administration of longer acting insulin if necessary, diabetics may be able to omit lunch or greatly reduce the size of that meal, and thereby avoid the need for midday insulin.

The delayed adsorption of nutrients when both GLIP and insulin are administered before breakfast will also reduce the risk of hypoglycaemia if lunch is delayed.

The studies described herein also indicate that a therapeutic regimen including both GLIP and insulin will in many cases permit the use of reduced doses of insulin. This is also beneficial in the avoidance of hypoglycaemia.

GLIP or its related peptides which may be employed in the treatment methods described herein may be administered orally, nasally or parenterally. Parenteral administration may be by a variety of routes including subcutaneous or intravenous infusion, and subcutaneous or intravenous injection.

The regimen of GLIP or GLIP and insulin administration required to give the desired glycaemic control in a diabetic patient can be readily determined by those skilled in the management of diabetic patients.

As will be understood by those skilled in the art, any suitable insulin preparation may be used in conjunction with GLIP administration in the combined regimen described herein.

Suitable insulins include regular or fast-acting insulin to maintain blood glucose control through the post-prandial interval, with or without addition of longer-acting insulin to maintain blood glucose control through the post-absorptive interval.

The dosages of GLIP required may be optimised for each subject by evaluation of the degree of glycaemic control achieved by trial doses.

Another convenient method of monitoring the level of effect of GLIP on a subject is to monitor the blood level of pancreatic polypeptide in response to trial doses of GLIP.

Such dosage and regimen adjustments are now commonplace, for example for diabetics treated with mixtures of fast and slow acting insulins. These mixed

preparations are available in various ratios of fast to slow and an appropriate ratio must be selected for a particular patient by trial doses. One patient may even employ insulin preparations of different ratios to handle varying sizes of meals. By similar testing, a suitable GLIP and insulin regimen may be selected.

GLIP and insulin may be administered separately or may be prepared and administered as a single formulation.

EXAMPLES

Example 1

7 subjects with remission phase Type I diabetes were studied after ingestion of a standardised meal of Sustacal (Upjohn) (delivering 30 kg/kg). Subjects continued their normal insulin treatment programme on the day prior to the test and, on the day of the test, omitted their morning insulin injection and arrived fasting at 8:00 am. On one test day they were given the Sustacal meal, followed immediately by initiation of intravenous infusion of GLIP (synthetic human GLIP-(7-36)amide from Peninsula, U.K.) at an infusion rate of 1.2 pm/kg/min. Infusion was continued for 120 minutes. Blood levels of glucose, C-peptide, gastrin, glucagon and HPP were monitored by standard radioimmunoassay methods in samples taken before and at intervals during the study, up to 180 minutes. On another test day, subjects were given the Sustacal meal alone and the same analytes were similarly monitored.

Results are shown in Figure 1.

Example 2

Four subjects with remission phase Type I diabetes were studied during intravenous glucose infusion. Subjects prepared for the tests as described in Example 1, but received an intravenous infusion of glucose (20 g

over 60 min. constant rate) instead of the Sustacal meal. On one test day, they also received intravenous GLIP for 60 minutes (1.2 pm/kg/min for 60 min.) and on another test day, they received IV glucose alone. Blood levels of glucose and C-peptide were monitored as in Example 1.

The results are shown in Figure 2.

Example 3

Four subjects with remission phase Type I diabetes were studied during infusion with 0.75 pm/kg/min GLIP for 120 minutes after a Sustacal meal.

The test was conducted as described in Example 1 and blood glucose and C-peptide levels were measured. On a further test day, the subjects were studied during saline infusion after a similar Sustacal meal.

Results are shown in Figure 3.

Example 4

7 normal volunteers were studied after ingestion of a Sustacal meal either alone or immediately preceded by a subcutaneous injection of 100 μg GLIP.

Results are shown in Figure 4. *indicates statistically significant differences between treatments ($p<0.05$).

A delay in increase in blood levels of glucose, HPP, C-peptide and insulin was seen. When the experiment was repeated with 50 μg or 200 μg dose of GLIP, proportionally shorter and longer delays, respectively, were seen.

Example 5

7 Type I diabetic subjects were studied. Subjects omitted their morning insulin injection on the days of the tests and were given a Sustacal meal alone one day and, on another day, a Sustacal meal immediately preceded by a subcutaneous injection of 100 μg GLIP.

The results are shown in Figure 5. *indicates statistically significant differences between treatments ($p<0.05$).

Example 6

One Type 1 diabetic subject was given GLIP along with insulin and the effects on post-prandial glycaemia observed. The subject received 5 units of insulin and 50 μg GLIP as subcutaneous injections immediately prior to ingestion of a Sustacal meal as described in Example 1. The results are shown in Figure 6. Blood levels of GLIP were monitored by a standard radioimmunoassay method.

Although only preferred embodiments of the present invention have been described, the present invention is not limited to the features of these embodiments, but includes all variations and modifications within the scope of the claims.

I CLAIM:

1. A method of treating insulin-requiring diabetes in a mammal comprising administering to the mammal in a suitable regimen an effective amount of insulin and an effective amount of a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b).

2. The method of claim 1 wherein the mammal is a human.

3. The method of claim 2 wherein an effective amount of insulin and an effective amount of a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b)

are administered to the human at a selected time prior to ingestion of a meal.

4. The method of any of claims 1 to 3 wherein the insulin-requiring diabetes is Type I diabetes.

5. The method of any of claims 1 to 3 wherein the insulin-requiring diabetes is Type II diabetes.

6. Use of a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b)

for the preparation of a medicament for use in the treatment of insulin-requiring diabetes in a suitable

regimen which additionally comprises treatment with insulin.

7. Use of a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b) for the preparation of a medicament which also includes insulin for treatment of insulin-requiring diabetes.

8. Use of a peptide in accordance with claim 6 wherein the insulin-requiring diabetes is Type I diabetes.

9. Use of a peptide in accordance with claim 7 wherein the insulin-requiring diabetes is Type I diabetes.

10. A pharmaceutical composition for the treatment of insulin-requiring diabetes comprising an effective amount of a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b) and a pharmaceutically acceptable carrier.

11. A pharmaceutical composition in accordance with claim 10 for the treatment of Type I diabetes.

12. The pharmaceutical composition of claim 10 or 11 further comprising an effective amount of insulin.

13. A method of treating Type I diabetes in a mammal comprising administering to the mammal an effective amount of a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b).

14. Use of a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b)

for the preparation of a medicament for use in the treatment of Type I diabetes.

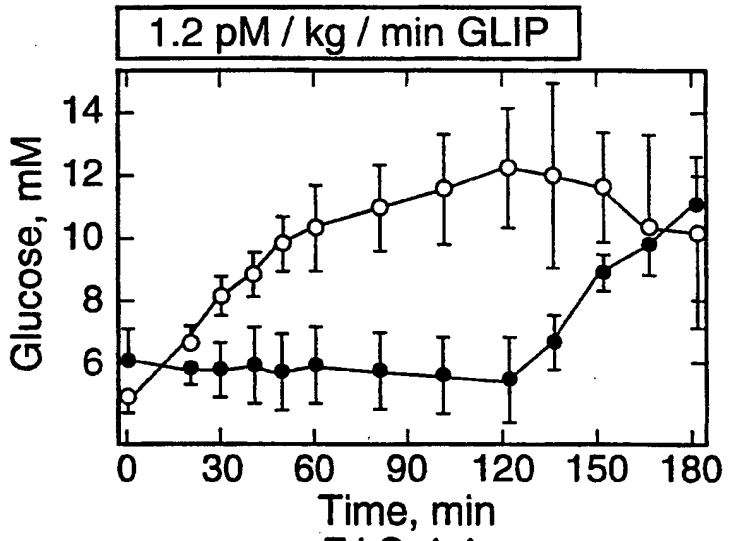

FIG.1A.

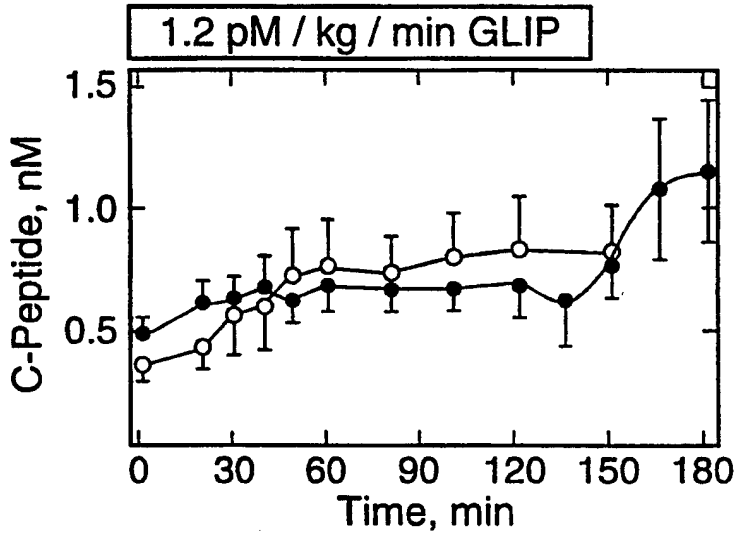

FIG.1B.

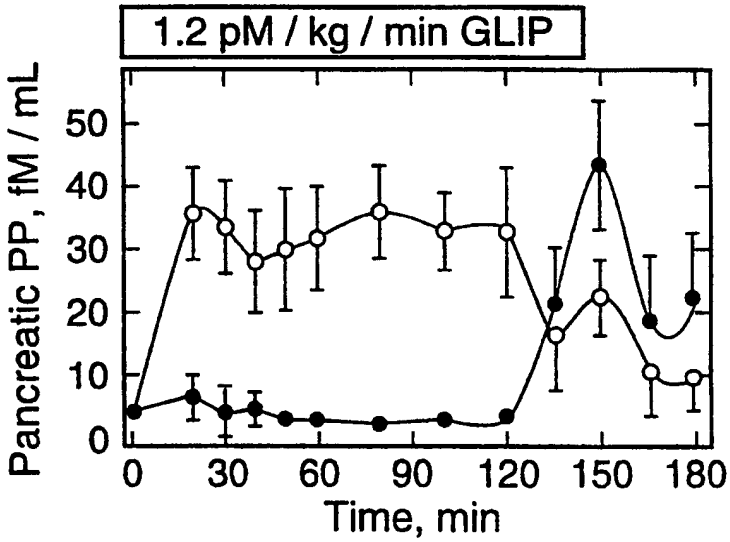

FIG.1C.

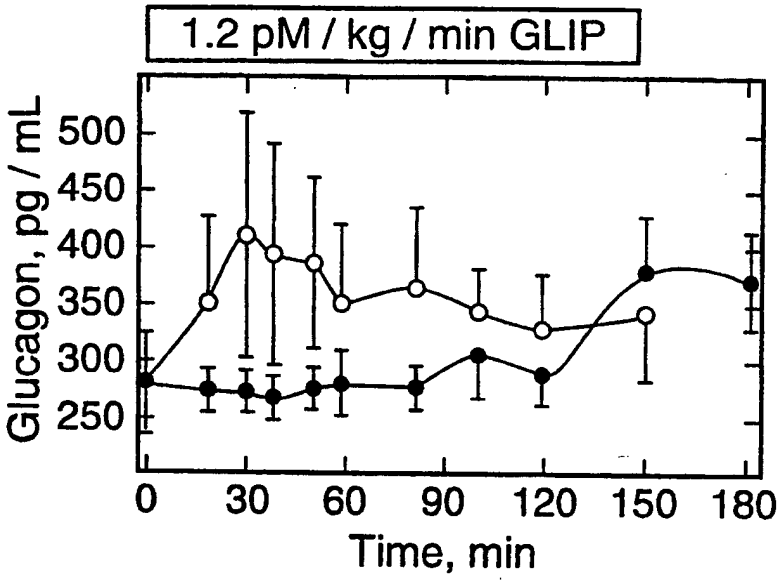
1.2 pM / kg / min GLIP
Glucagon, pg / mL
500
450
400
350
300
250
0
30
60
90
120
150
180
Time, min

FIG.1D.

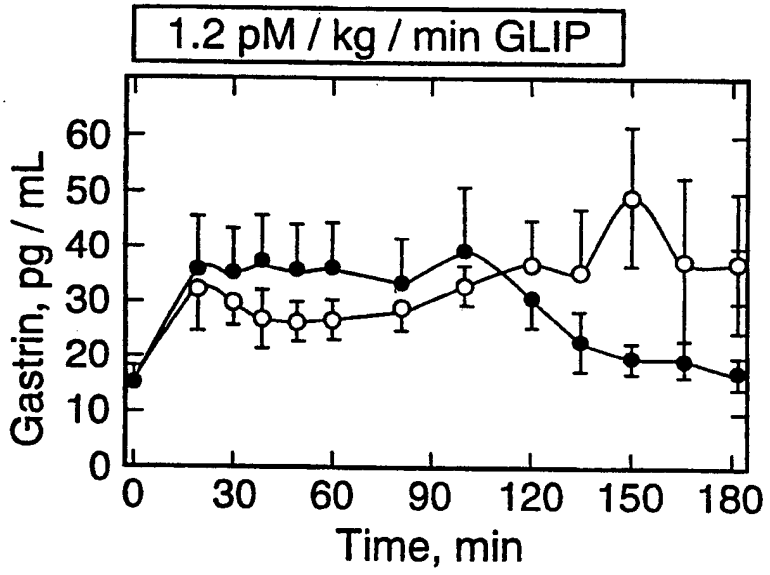
1.2 pM / kg / min GLIP
Gastrin, pg / mL
60
50
40
30
20
10
0
0
30
60
90
120
150
180
Time, min

FIG.1E.

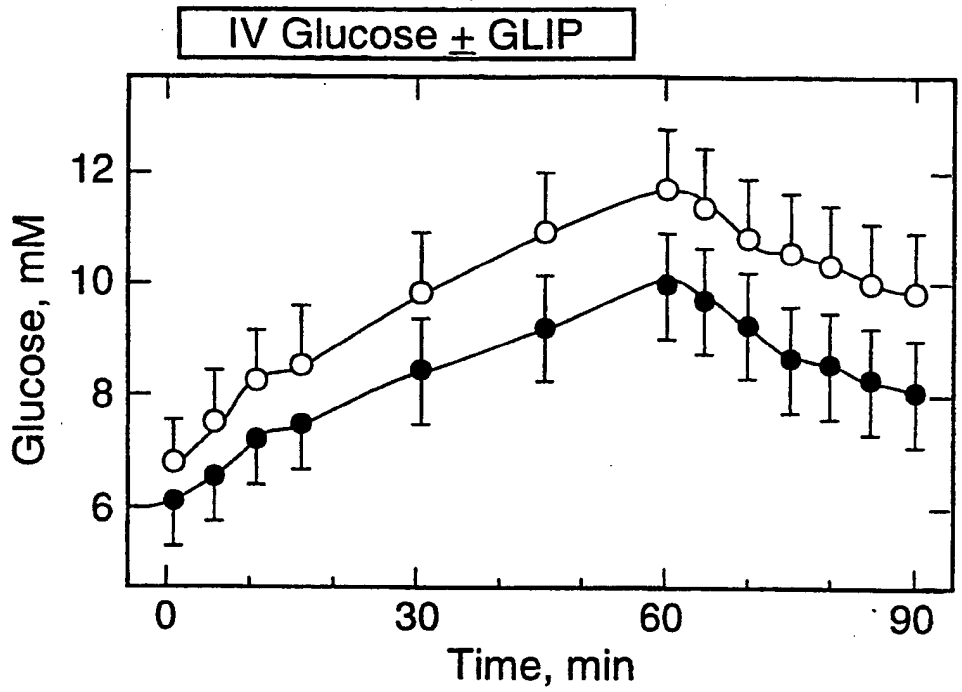
IV Glucose ± GLIP
Glucose, mM
12
10
8
6
0
30
60
90
Time, min

FIG.2A.

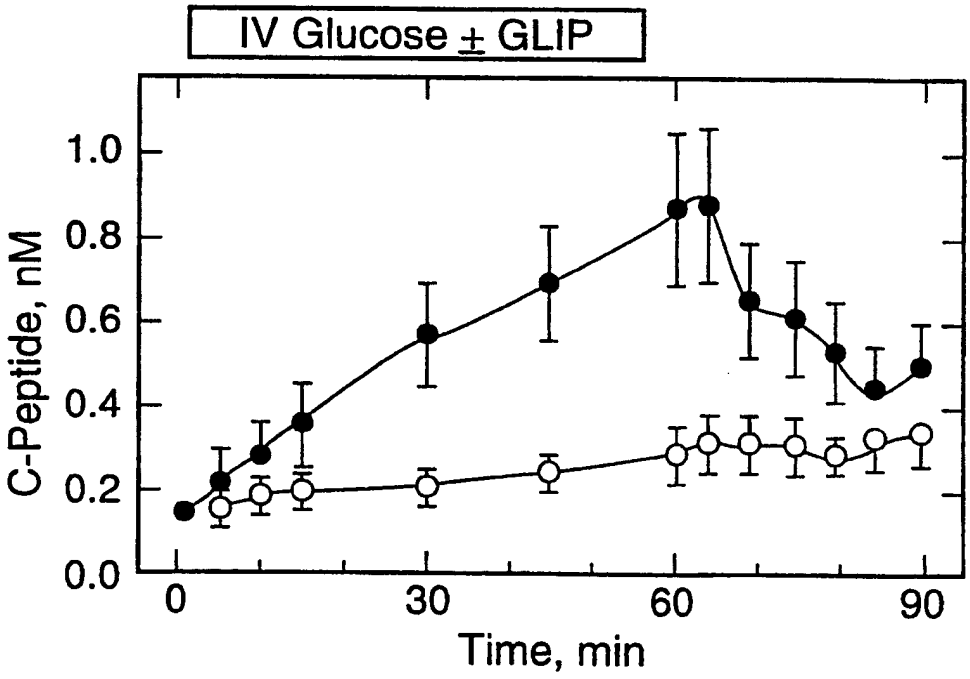
IV Glucose ± GLIP
C-Peptide, nM
1.0
0.8
0.6
0.4
0.2
0.0
0
30
60
90
Time, min

FIG.2B.

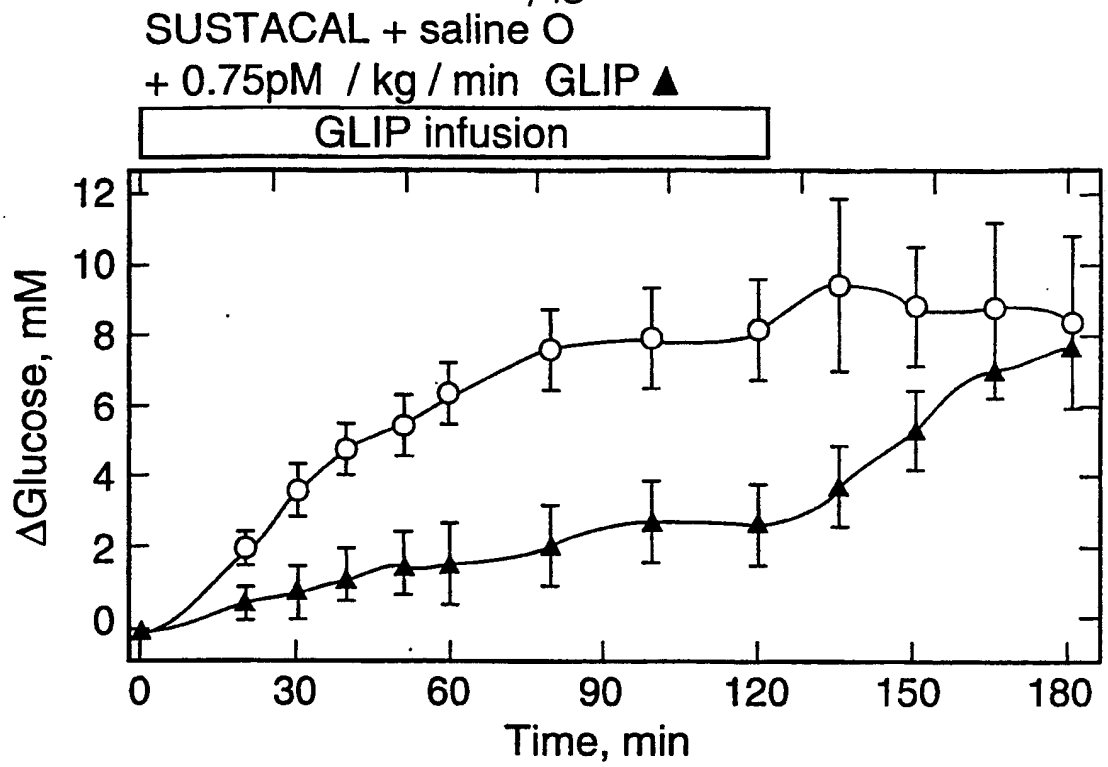
SUSTACAL + saline O
+ 0.75pM / kg / min GLIP ▲
GLIP infusion
ΔGlucose, mM
12
10
8
6
4
2
0
0
30
60
90
120
150
180
Time, min

FIG.3A.

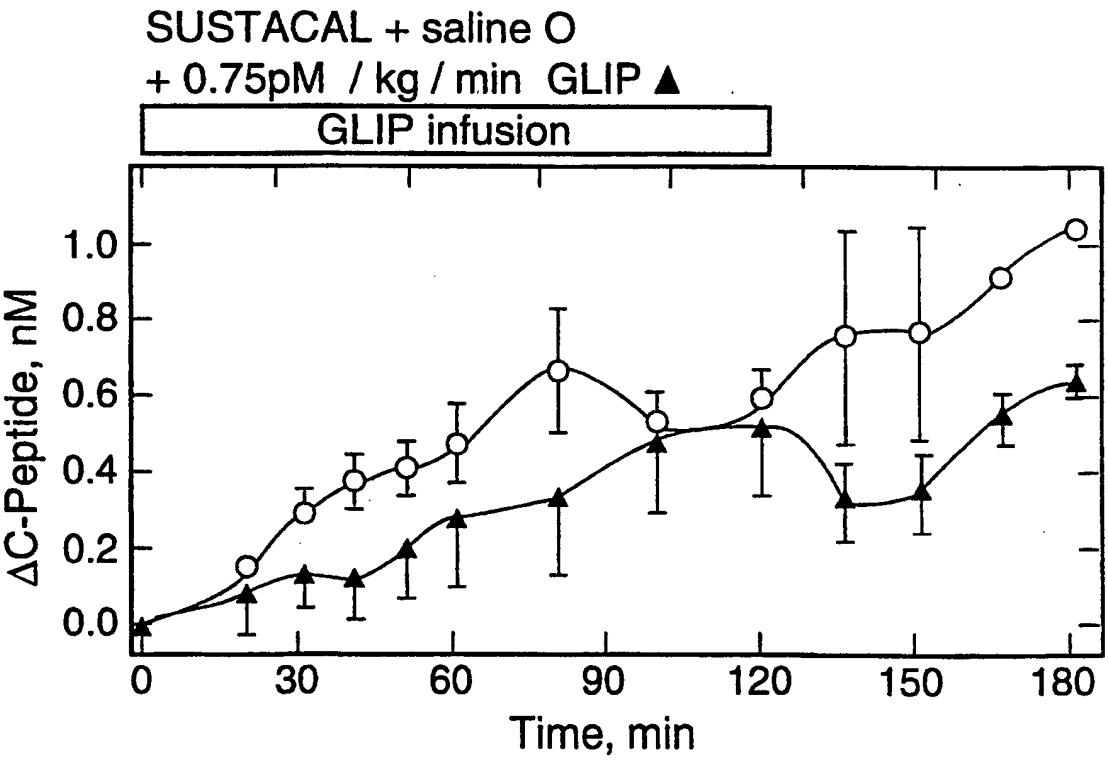
SUSTACAL + saline O
+ 0.75pM / kg / min GLIP ▲
GLIP infusion
ΔC-Peptide, nM
1.0
0.8
0.6
0.4
0.2
0.0
0
30
60
90
120
150
180
Time, min

FIG.3B.

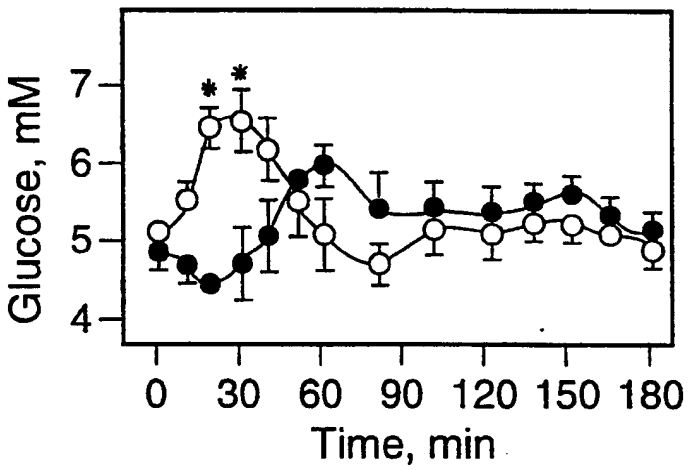
Glucose, mM
7
6
5
4
*
*
0
30
60
90
120
150
180
Time, min

FIG.4A.

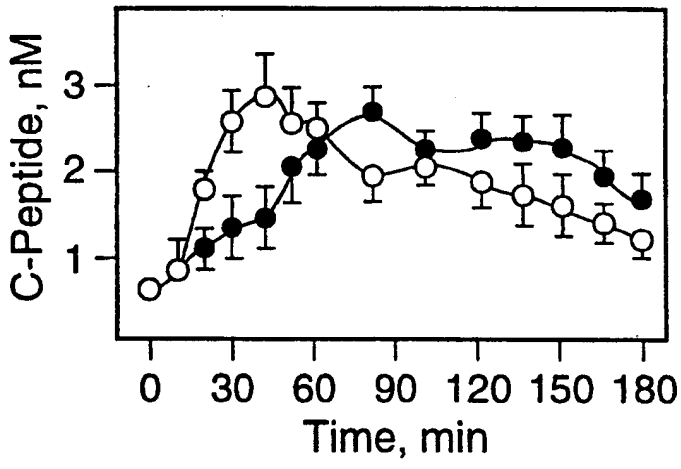
C-Peptide, nM
3
2
1
0
30
60
90
120
150
180
Time, min

FIG.4B.

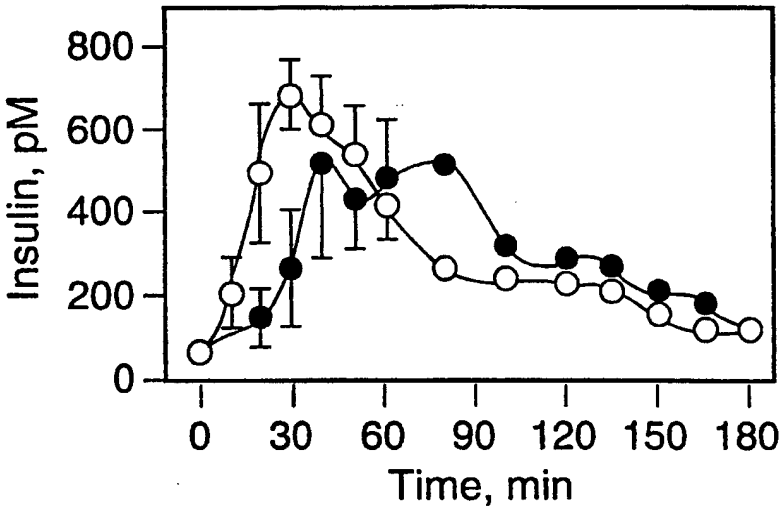
800
600
400
200
0
Insulin, pM
0
30
60
90
120
150
180
Time, min

FIG.4C.

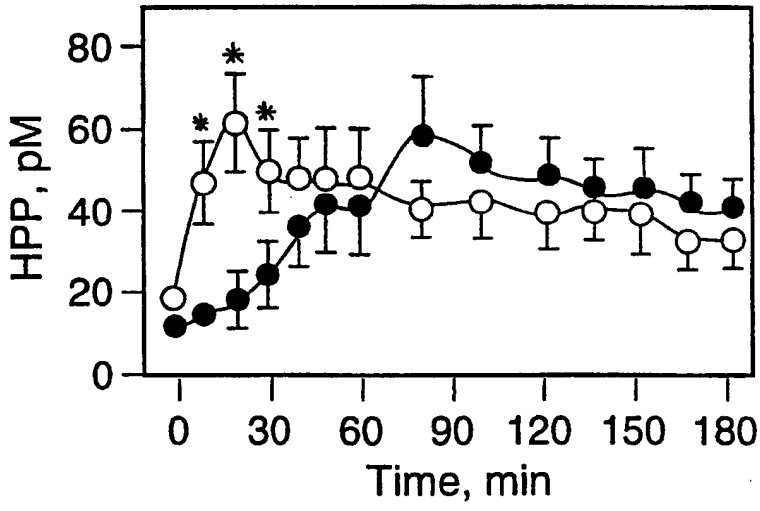
80
60
40
20
0
HPP, pM
*
*
*
0
30
60
90
120
150
180
Time, min

FIG.4D.

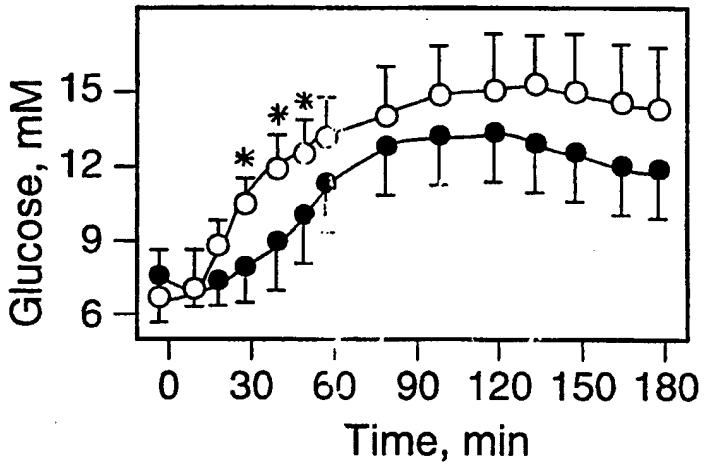
Glucose, mM
15
12
9
6
0 30 60 90 120 150 180
Time, min

FIG.5A.

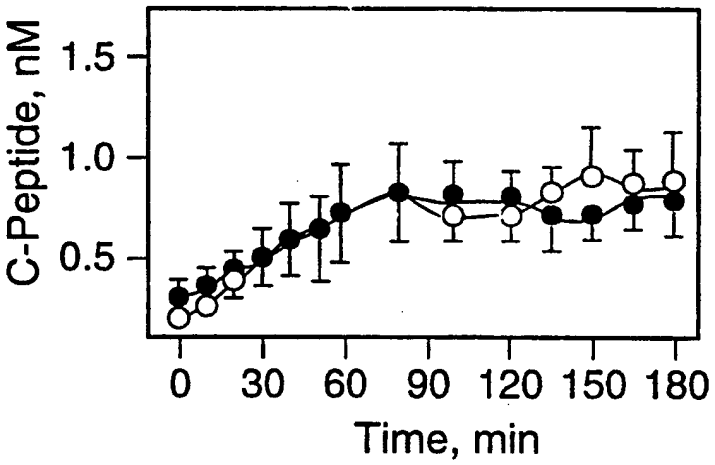
C-Peptide, nM
1.5
1.0
0.5
0 30 60 90 120 150 180
Time, min

FIG.5B.

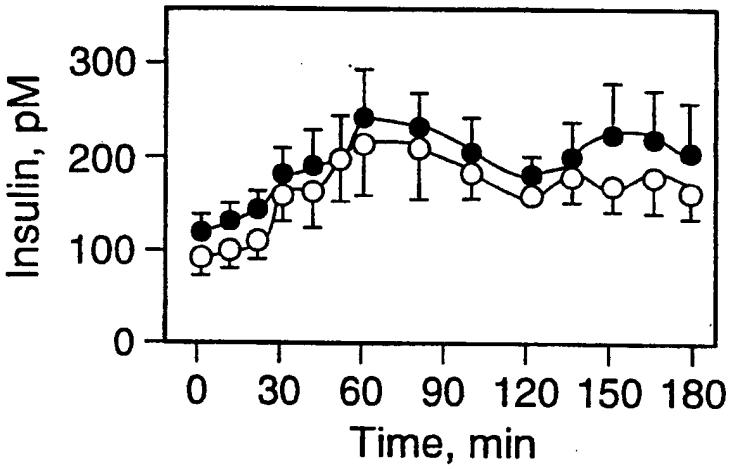
Insulin, pM
300
200
100
0
0 30 60 90 120 150 180
Time, min

FIG.5C.

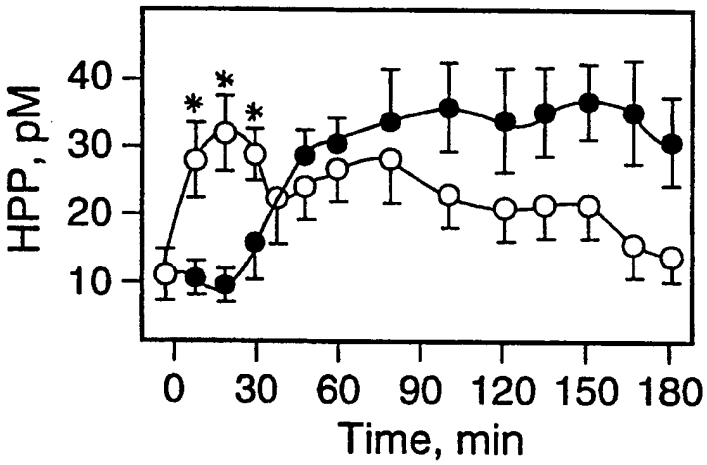
HPP, pM
40
30
20
10
*
*
*
0 30 60 90 120 150 180
Time, min

FIG.5D.

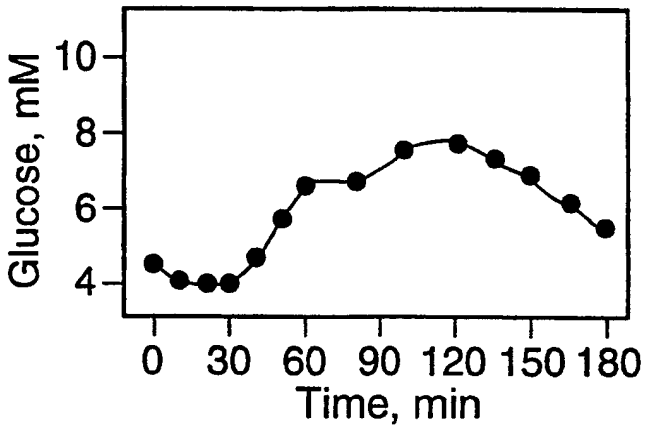

FIG.6A.

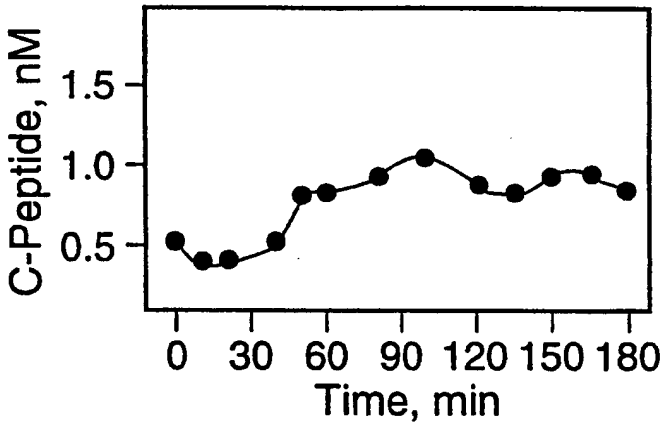

FIG.6B.

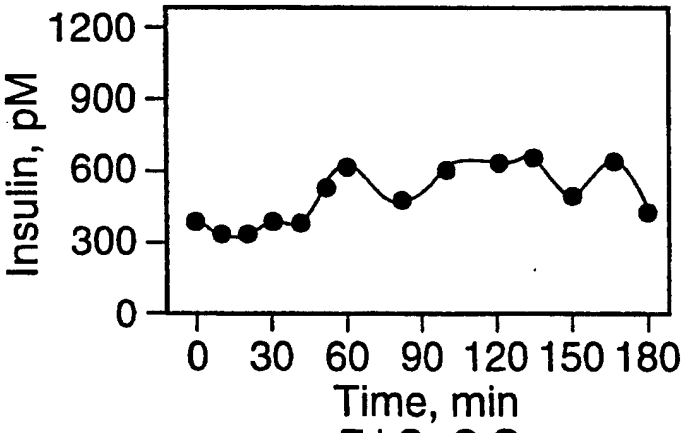

FIG.6C.

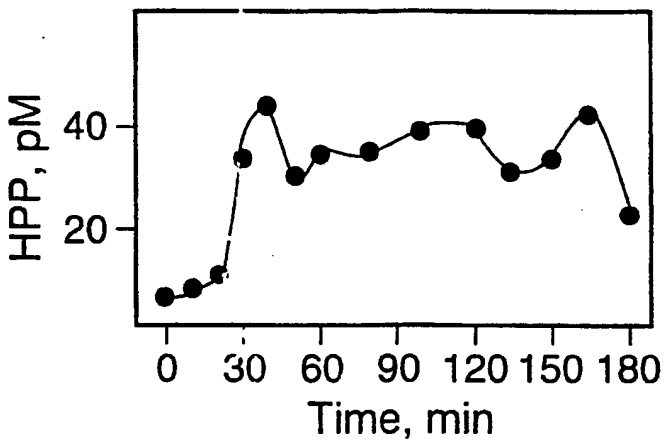

FIG.6D.

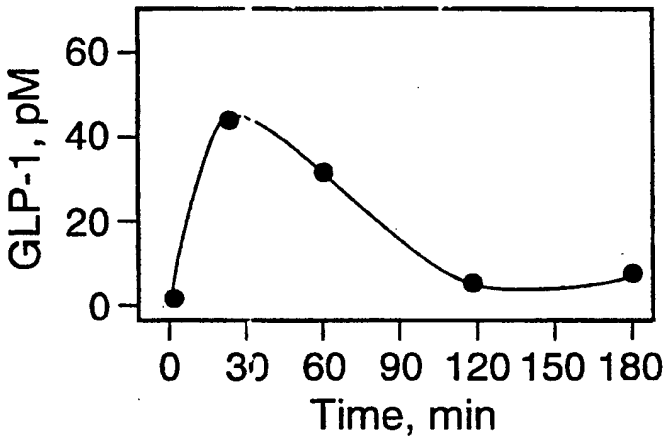

FIG.6E.

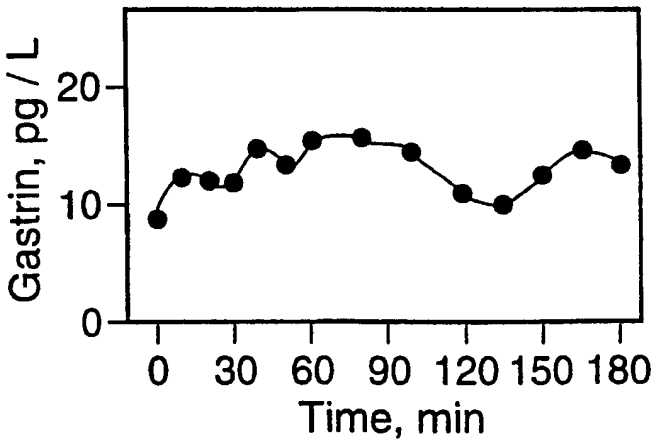

FIG.6F.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/CA 95/00287

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/26 //(A61K38/26,38:28)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO-A-91 11457 (BUCKLEY D. ET AL.) 8 August 1991 see the whole document ---	1,5,6
X	THE JOURNAL OF CLINICAL INVESTIGATION, vol. 93, no. 5, May 1994 pages 2263-2266, D'ALESIO D.A. ET AL. 'Glucagon-like Peptide 1 Enhances Glucose Tolerance Both by Stimulation of Insulin Release and by Increasing Insulin-independent Glucose Disposal' see the whole document --- -/--	1-14

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 July 1995	07.08.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Moreau, J

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/CA 95/00287

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THE NEW ENGLAND JOURNAL OF MEDICINE , vol. 326, no. 20, 14 May 1992 BOSTON (US), pages 1316-1322, GUTNIAK M. ET AL. 'Antidiabetogenic effect of glucagon-like peptide-1 (7-36)amide in normal subjects and patients with diabetes mellitus' cited in the application see the whole document	1-14
A	WO-A-93 25579 (PFIZER INC.) 23 December 1993 see the whole document	1-14

1

INTERNATIONAL SEARCH REPORT

i national application No.
PCT/CA95/00287

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-5,13
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-5,13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter nal Application No
PCT/CA 95/00287

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9111457	08-08-91	EP-A-	0512042	11-11-92
WO-A-9325579	23-12-93	AU-B-	4027593	04-01-94
		CA-A-	2138161	23-12-93
		CN-A-	1085913	27-04-94
		EP-A-	0646128	05-04-95
		HU-A-	64367	28-12-93
		JP-T-	7504679	25-05-95
		NO-A-	944853	14-12-94